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Methodological Review

Multivariate image analysis in biomedicine

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Abstract

In recent years, multivariate imaging techniques are developed and applied in biomedical research in an increasing degree. In research projets and in clinical studies as well *m*-dimensional multivariate images (MVI) are recorded and stored to databases for a subsequent analysis. The complexity of the *m*-dimensional data and the growing number of high throughput applications call for new strategies for the application of image processing and data mining to support the direct interactive analysis by human experts. This article provides an overview of proposed approaches for MVI analysis in biomedicine. After summarizing the biomedical MVI techniques the two level framework for MVI analysis is illustrated. Following this framework, the state-of-the-art solutions from the fields of image processing and data mining are reviewed and discussed. Motivations for MVI data mining in biology and medicine are characterized, followed by an overview of graphical and auditory approaches for interactive data exploration. The paper concludes with summarizing open problems in MVI analysis and remarks upon the future development of biomedical MVI analysis.

Keywords: Multimodal imaging; Optical microscopy; Medical imaging; Data Mining; Explorative data analysis; Artificial neural networks; Man–machine interaction; Multimodal display

1. Introduction

In recent years we observe an increasing number of biomedical imaging applications that associate a number of m signal values to pixel or voxel coordinates $\mathbf{p}$ in a two- or three-dimensional array (i.e., $\mathbf{p} = (x, y)$ or $= (x, y, z)$, respectively). In the result stack of m intensity images, m locally corresponding signal values $s_1, \ldots, s_m$ are associated to a pixel (or voxel) $\mathbf{p}$ and can be interpreted as a point $\mathbf{s}(\mathbf{p}) = (s_1, \ldots, s_m)$ in an m-dimensional space. Without loss of generality, we assume that the signals are subject to a post-imaging normalization step and mapped to an appropriate scale $s_i \in [0;1]$. This mapping procedure often includes the application of a log function to enhance weak signals and/or a rescaling of the vector components s_i to have zero mean and unit variance. In this article, such imaging approaches are referred to as biomedical *multivariate* imaging, i.e., techniques for recording multivariate images or volumes.

In microbiology, researchers analyze MVIs to corelate different molecular parameters locally in cells and tissue specimens. The *local* identification of molecules is enabled by ongoing advances in the development, understanding, and optimization of monoclonal antibody markers (mAb). In addition, advanced staining techniques, multiband imaging, and color decomposition [1] allow simultaneous visualization of macromolecules in the cells (e.g., [2–4]). This simultaneous identification of molecules by selective visualization, enables quantitative studies on a large scale, resulting in a new perspective on optical microscopy as a tool for quantitative studies in microbiological research which can be interpreted as a renaissance of optical microscopy [5–7]. The imaging approaches are applied to cell samples from different specimens, in certain stress

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conditions, or with different pharmaceutical treatment to get more comprehensive descriptions of spatial and temporal molecular dynamics in the cell [8]. But not the molecular visualization capacities have been advanced only, the implementation of highly standardized protocols through the application of modern robotics and personal computers pave the way to a new level of experiment automation [9]. Thus, cellular parameters can be simultaneously and locally identified in high-throughput screening (HTS) approaches.

Another group of MVI techniques is based on combining different imaging *modalities* by merging registered images from different devices, which is usually referred to as *intermodular* imaging. In microbiology for instance, microscopy and magnet resonance imaging (MRI) can be combined to get new insight into cell structure [10].

However, multivariate imaging is developed and applied much more frequently in the field of medical imaging. In this article, the term *medical imaging* comprises imaging techniques applied to macrobiological structures in the context of medical diagnosis. The imaging techniques are ultrasonic imaging, X-ray imaging, computer tomography (CT), single photon emission CT (SPECT), positron emission tomography (PET), and MRI [11–14]. Although a few multivariate imaging systems are already in clinical use, MVI based diagnosis is still more regarded a field of research than a standard diagnostic imaging technique.

The approaches can be subdivided into intramodular and intermodular ones. Intramodular imaging applies m different parameterizations of one imaging technique to record a set of m images. One favorable advantage of this approach is, that the m images usually have identical spacial resolution and the registration of the images is feasible. One example of intramodular multivariate imaging is multispectral microscopy imaging, which has been successfully applied in skin lesion classification [15]. Another group of intramodular imaging approaches is based on applying MRI with different protocols. In so called multispectral MRI, a T1-, T2-, and proton density weighted image is recorded for brain studies. In another brain study context, so called dynamic functional MRI (fMRI) and diffusion tensor imaging [16] is applied. In the latter case, a number of diffusion weighted MRI plus one reference image is recorded to visualize the microscopic water motion in the brain. In cancer diagnosis, dynamic contrast enhanced MRI (DCE MRI) [17,18] is applied to visualize vascular features of suspicious lesions. A time series of MRI volumes is recorded, and the tissue parameters are characterized by the signal dynamics, which are affected by an injected paramagnetic contrast agent. Combinations of multispectral and contrast enhanced MRI is applied for multiple sclerosis analysis [19] and breast lesion diagnosis [20].

The second group of intermodular approaches use different imaging techniques, usually based on different physical effects. The recordings usually differ in spacial resolution, signal scales and are sometimes recorded with a considerable time lag in between. Thus, the co-registration of the images becomes a difficult scientific problem. Usually, this problem is solved by tuning the imaging parameters to adjust the spacial resolutions and by applying registration algorithms. The first is done by tuning the imaging sequence in MRI or applying special filters in CT or PET. Several intermodular imaging approaches have been reported, among them are most recently PET/CT [21] or CT/MRI/PET [22].

Although open source software is available for examining multimodal image data [23], the growing number of research projects and diagnosis systems that employ multivariate images (MVI) and the data complexity results in a call for new approaches for interpretation, which has not been answered yet, as to the best of the author's knowledge and as also reported in [21].

This article reviews the methods that have been proposed for MVI analysis. The review is oriented along a two level analysis framework which is outlined in the following. The first level of analysis is called the *exploration level* or E-level (see Fig. 1). The image content, i.e., the pixel or region parameters $\mathbf{s}$ are displayed and a user perceives displays from different MVI (or different regions in one MVI). Through interactive browsing of image regions of interest (ROI), knowledge is discovered on the same level intention-driven as by serendipity. Since all m images cannot be displayed in an instant, the images have to be processed to adapt the content of the images to the perceptual skills of the human user. To this end, visualization algorithms are needed that account for the statistical features in the MVI.

In the second level, quantitative image parameters $\mathbf{u}_{(i)} \in \mathbb{R}^d$ of ROIs are extracted from the image and analyzed full-automatically (see Fig. 1). The extraction step can be realized full-automatically or with some user-interaction. In both ways, the extraction process needs to be highly standardized since reproducibility of this step is crucial. The extracted data are stored to a database. The ROI parameters $\mathbf{u}^{(i)}$ are computed from the signal values $\mathbf{s}(\mathbf{p})$ and describe biological parameters quantitatively. In a basic set up, each pixel $\mathbf{p}$ is considered as a ROI: $\mathbf{u}^{(i)} = \mathbf{s}(\mathbf{p})$ and $d = m$. Afterwards, statistical data mining methods are applied to find and prove hidden structures and regularities in the data, e.g., clusters. The entire level is referred to as the *statistical level* or S-level. Usually, the user provides some background information and ideas about the data structure, so serendipity-driven discoveries are more exceptional. Examples for labels are sample treatment parameters, the gender or age of a patient, or a TNM-class label[1] for instance. In this article, all kinds

[1] TNM is a classification system for tumors, defined by the UICC (Union Internationale contre le Cancer), TNM = Tumor, Node, Metastasis.

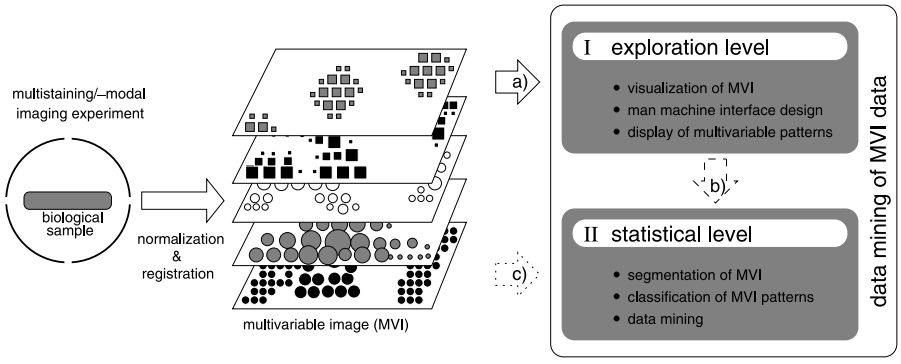

Fig. 1. Interpretation of multivariate images (MVI) is done in a two level process. (a) After preprocessing the images, the content is visualized and analyzed through direct visual inspection. (b) In a next step, quantitative data are extracted from the images and analyzed applying data mining methods. A direct, full-automatically data mining application (c) is less usual, because the image quality and the content of the recorded images changes considerably between different images, even under the application of a highly standardized protocol.

of such labels will be referred to as *meta-labels* $y^{(j)}$. The index j usually identifies an index of a ROI or an entire MVI. The S-level needs data mining methods, that can be applied to sets of extracted parameter vectors to localize interesting ROIs, detect interesting patterns $\mathbf{u}^{(i)}$ or components u_k, $k \in \{1,\ldots,d\}$. The complete two level framework for MVI analysis is illustrated in Fig. 1. To realize the E- and the S-level components, methods from the fields of image processing and data mining have been proposed, which are summarized in the following sections.

2. Image processing issues in MVI analysis

Following the image recording and signal normalization, image processing algorithms are applied to prepare the MVI data for the evaluation in the E- or S-level.

Each step in MVI analysis naturally depends on a spatially and/or temporally co-registration of the images from different sources. Registration employs sophisticated mathematical aligning algorithms to associate signals from different recordings according to a selected optimization criterion. The importance of registration for all following steps can be illustrated by a look on the number of related papers, referenced in PUBMED. In Fig. 2 the gray histogram shows the number of papers that include the terms "multimodul* AND registration" within their title or abstract. Although this procedure can give just an idea about the true relevance of this matter, the plot illustrates nicely the growing importance of multimodular registration. In addition, one can see, that the number of papers containing "multimodul* AND segmentation" seems to stay constant and small in relation to the registration related papers. This may be explained by the fact, that without a satisfying registration, MVI segmentation can not be applied successfully.

Registration algorithms can be categorized according to transformation elasticity or the degree of using external information (like markers). In intermodular registration, mutual information is reported to be an applicable optimization criterion [24]. In the particular case of multimodal brain MRI segmentation Viergever argues to use rigid registration for intermodular registration and elastic registration for intramodular registration [25,22].

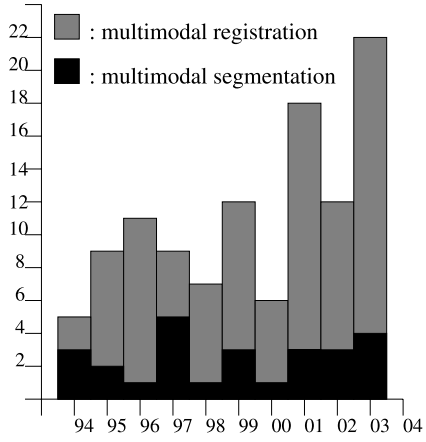

Fig. 2. The numbers of papers about multimodular registration (gray boxes) or multimodular segmentation (black boxes) are plotted for the last ten years as referenced by PUBMED.

Following the registration the user is to be provided with a display, that represents the entire MVI and can be used as a *navigation map* for browsing in the E-level (illustrated in Fig. 3). The particular approach for computing the navigation map is to be chosen according to the availability of background knowledge regarding the image content. Two different situations can be identified: First, meta-labels of the images are provided by a biomedical expert. This is for example in many macrobiological applications the case, where a considerable amount of knowledge is used to tune the visualization process. This explicit knowledge includes for instance anatomy, signal intensity scales for certain types of matter, or the number of different object classes in the

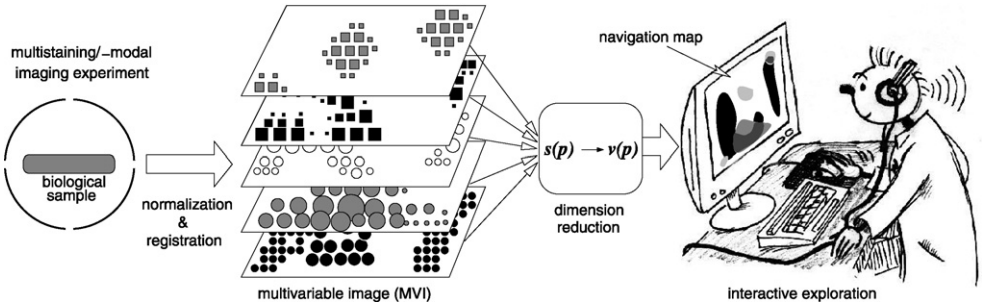

Fig. 3. One way of exploring the MVI stack is to compute a navigation map by dimension reduction techniques. The m-dimensional signal vectors $\mathbf{s}(\mathbf{p})$ are mapped to a much lower dimensional one $\mathbf{v}(\mathbf{p}) \in [0;1]^n$. The lower dimension ($n = 1, 2, 3$) allows straight forward display of the map in gray value or RGB mode. The image is displayed to a user who can interactively browse through the image and activates graphical or auditory displays of the m-dimensional patterns.

image. Consider, e.g., brain imaging with MRI separating white/gray matter, cerebrospinal fluid (CSF), bone plus an additional class like a lesion. The second situation is characterized by the absence (or an intended exclusion) of any meta-labels. In this case, the navigation map is computed applying *dimension reduction* techniques to the data. The easiest method is to compute gray value images $g(\mathbf{p})$ from the entire image stack by pointwise evaluating the signal values applying a simple function $g(\mathbf{s}(\mathbf{p}))$. The function can be defined as the maximum value $g(\mathbf{p}) = \max_i\{s_i(\mathbf{p})\}$ through the stack or the total sum of signal intensities $g(\mathbf{p}) = \sum_i s_i(\mathbf{p})$. More sophisticated algorithms have been proposed in the fields of statistics, pattern recognition, machine learning (ML), and artificial neural networks (ANN). The most prominent are principal component analysis (PCA), multi-dimensional scaling (MDS), projection pursuit (PP), self-organized maps (SOM), independent component analysis (ICA), kernel PCA (kPCA), and local-linear embedding (LLE). Each method facilitates a projection from the m-dimensional signal space into a lower-dimensional spaces

$$P : \mathbf{s}(\mathbf{p}) \mapsto \mathbf{v}(\mathbf{p}), \quad \mathbf{s} \in [0;1]^m, \quad \mathbf{v} \in \mathbb{R}^n, \text{ with } n < m$$

according to statistical features of the dataset, for instance the data variance (PCA), statistical independence (ICA) or the data topology (SOM, LLE). Although these techniques have been applied in numerous engineering and data mining applications, applications to biomedical imaging domains are still reported rather exceptional [19]. One reason is, that displays based on these techniques show more statistical features in the data and less biological qualities. The future task in realizing inter- and multidisciplinary research in the context of biomedical MVI must be to apply, evaluate, and discuss the methods in this field.

To extract quantitative parameters $\mathbf{u}^{(i)}$ from the data for the S-level, image segmentation is applied. Segmentation can be described as a pixel labeling function $L : (\mathbf{p}) \mapsto l$, $l \in \{0, \ldots, c\}$, i.e., each image pixel is assigned to a label, that describes its membership to a region of similar features. This region can be a cell compartment, a cell body, a tissue class or a matter class.

The features can be the raw signal values $\mathbf{s}(\mathbf{p})$ or some image features like signal intensity or texture, that are computed from the original values $\mathscr{F} : \mathbf{s} \mapsto \mathbf{f}(\mathbf{s})$, $\mathbf{f} \in \mathbb{R}^k$. Note, that $\mathscr{F}$ is usually defined on the signal values in one pixel $\mathbf{s}(\mathbf{p})$ *or* on a pixel neighborhood. The labeling can be regarded as a part of a classification procedure, if the regions are biological significant objects, for example, cell bodies of different type or tissue classes. The number of classes, that are to be represented with labels vary between biomedical domains. In the majority of applications, a number of n biological objects is separated from the background (Fig. 4A) and also distinguished from each other:

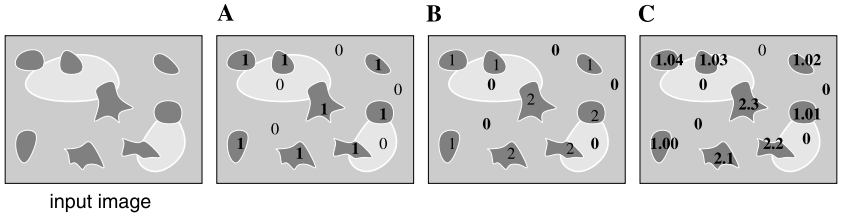

Fig. 4. A MVI is segmented into regions of similar features to support data mining in the E- and S-level. Depending on the biomedical question at hand, images can be segmented into (A): object(1) background(0), (B) objects classes (n) and background (0), (C) entities of object classes ($n.m$). Note that background (0) can consist of different biological objects classes.

$$L(\mathbf{p}) = \begin{cases} l & \text{if } \mathbf{p} \text{ is covered by object } l, (l = 1, \ldots, c), \\ 0 & \text{if } \mathbf{p} \text{ belongs to background.} \end{cases} \quad (1)$$

Note, that the label l can be *anything* between an object class (0 = background; 1, 2 = covered by cell of type 1 or 2, see Figs. 4B and C), and the index of a particular object from one class (Fig. 4D). Which is for example the case, if the positions and bodies of objects from one class is the essential quantitative information in the MVI.

The majority of the segmentation approaches in biomedical image analysis is concerned with the segmentation of macrobiological structures like tissue, organs, and bones in medical imaging domains. Comprehensive overviews of this field are published and discussed regularly [13,14,26]. Currently, researchers seem to focus on combinations of established segmentation algorithms (e.g., deformable models) with ML methods [27] and on so called spectral clustering algorithms [28].

In contrast, image segmentation in optical microscopy is much less reported. But to stay abreast of the growing importance of digital microscopy, a short overview is given below.

The processing of digital micrographs is characterized by individual problems, some already identified in [29,30]. In each application, at least one of the following problems has to be addressed:

- inhomogeneous illumination across the selected visual field,
- occlusion of objects,
- variation of shape and/or size and/or orientation,
- variation of the signal intensity of objects from the same class.

Nevertheless, even if these problems have special characteristics in the domain of digital micrographs, they have already been identified in related occurrence and discussed in the computer vision community as fundamental problems, those can only be solved by employing certain heuristics (about size, shape, and color of the objects in the image) or by tuning the general framework of the imaging (the light sources, for instance). But in biomedical imaging, the problems are often more difficult to solve, because much less heuristics can be made about the signal intensities or object shapes. Also the imaging framework itself can be standardized only to a limited extend, because the visualization of microbiological structures is a rapidly evolving field.

One large fraction of algorithms for automatic micrograph segmentation can be summarized as model-based approaches. Those are based on circle or ellipsoid detection objective Hough-transforms [31,32], wave-propagation [33], deformable models or snakes [34] or iterative grouping of image primitives [35–38]. Recently, some works have been published to learn Hough-transform parameters for arbitrary shapes from a set of labeled data [39]. Another class of algorithms perform segmentation by computing a binary image, which is achieved by flooding schemes, morphological operators, and thresholding as proposed in [40–45]. Microscopy image processing algorithms based on ANN or ML are still rather exceptional and reported wide spread in the literature [46–52]. Due to the complexity of cell functions, which is rooted in the overwhelming diversity of expressed molecules and their relationships, a large diversity of the image domains is caused. The consequence of such diversity is, that publications are so wide-spread in the literature, i.e., through the fields of microscopy, biomedical engineering, biomedical imaging, bioinformatics, and pattern recognition that it is nearly impossible to get a comprehensive overview about the works in this field. As a matter of course, a wide spread of publications is not a problem unique to this field. But in case of micrograph segmentation it is considerably extreme. Note that neither an international meeting of this field is organized nor a journal is published regularly, that has a scope particularly defined in the microbiological imaging field. Altogether, microbiological image processing has *neither* made its way into standardized methodology like medical imaging with sonography, radiology or MRI *nor* even a scientific/engineering community exists that gathers at yearly meetings to discuss new approaches and evaluation principles for the algorithms. As a result the efforts and funding into the developments of evaluation software for micrographs is still small compared to the above listed "classic" medical imaging domains. In general, a full automatic segmentation is often considered so hard to achieve, that interactive segmentation systems are considered to be of substantial help for the labs [53–57].

Segmentation algorithms that take the multivariate features of the data into account are rather exceptional. The first multivariate images considered were multispectral MRI images from the head. Early works concerned about multimodal segmentation considered segmentation algorithms for single channels separately [58]. In [34] it is reported, that performing segmentation on just one image channel achieved most accurate results. The only works, taking all features into account employ clustering algorithms like in [59,60] for multispectral MRI images and more recently in [61] for the analysis of fMRI data. Another approach for intermodular segmentation employs probabilistic multiscale hierarchical segmentation [62] . Combining ANN approaches with active contours are again the focus of the researchers' attention [63].

Concluding this section, we can identify two open problems. First, since image processing is a substantial preprocessing step for the S-level, it becomes more and more important for researchers and engineers in the field

of microscopy image processing to build up platforms for communicating results, providing benchmark data and discussing evaluation frameworks. Second, although ANNs and ML have made their way into engineering with big success, their applications in the field of biomedical imaging in general and in MVI in particular is still exceptional. But bringing to mind these methods' potential for computing lower-dimensional data spaces or image segmentation (which both have been identified as essential steps in MVI interpretation) and their straightforward employment of meta-labels, one has to admit, that ANN and ML methods have to be considered more in the future.

3. Data mining in MVI

Data mining of MVI aims at identifying hidden regularities and unusual outliers in the high-dimensional data spaces with consideration of topological order. To this end, data mining methods are applied to support pattern classification or prediction by extracting patterns and describing data in a new comprehensible form. To choose the data mining approaches appropriately, the biomedical background of the MVI set must be considered. We will find, that data mining issues are differently motivated for the biological and medical domains.

3.1. Biological and medical background

In microbiology, we observe a growing world-wide attention to biological cells as complex functional units that act in networks and the call for new multidisciplinary approaches for modeling and understanding cells and cellular networks, employing biology, biophysics, and mathematics [64]. The basic aspect of employing multivariate optical microscopy in biomedicine is that the information about *spatial* correlations between the molecules is preserved, which is a valuable feature not owned by many other methods, as e.g., gel-electrophoresis or microarrays. The linkage of all informations shall culminate in the successful development of integrated models of cell functions. Simulation and graphical display of such models in virtual cells are corner stones in the rapid evolving field of systems biology [65]. In summary, MVI analysis is applied in microbiology to discover hidden regularities in patterns within one MVI or a set of MVIs (see Fig. 5) to gain deeper insights into the complex space of molecular cell functions. Since the images are generally recorded in an experimental set up background knowledge is limited and explicit meta-labels are exceptional.

MVI analysis in medical imaging is motivated from different developments. First, a growing number of laboratories and hospitals install state of the art picture archiving and communications systems (PACS) for realizing efficient storing, retrieving, and communicating in image data bases. Thus, large amounts of data together with diagnostic information are available. Second, the classic medical imaging technologies are further advanced towards (a) higher resolution, (b) increased sensitivity, (c) standardized protocols, and (d) increasing application fields. The developments (a)–(c) will allow merging data from different laboratories, as for instance in multicenter screening studies like [66]. Then, data mining can be applied to support the classification of medical image data, to analyze the imaging technique itself and/or to perform statistical analysis on large sets of quantitative parameters extracted from the images, for instance morphological parameters of tumors from a large number of cases (see Fig. 6).

Again, the choice of methods depends strongly on the availability of background knowledge and assumptions about interesting patterns. If the data are studied without background information, more attention is paid to realizing the E-level and methods from unsupervised

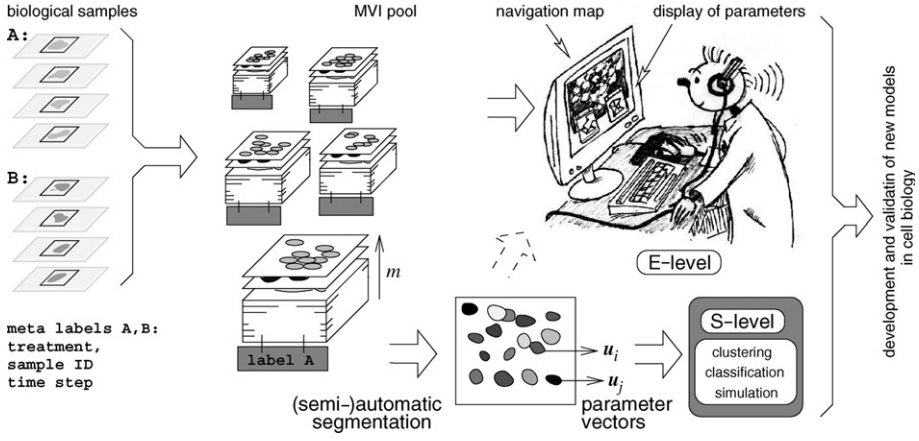

Fig. 5. MVIs are recorded for differently treated samples supplied with meta-labels. Data mining involves the direct inspection of local parameters $\mathbf{u}^{(i)}$ (E-level) to analyze the topological structure of the m-dimensional data in the sample. If segmentation is applied to the data, extracted numerical parameters are analyzed in the S-level.

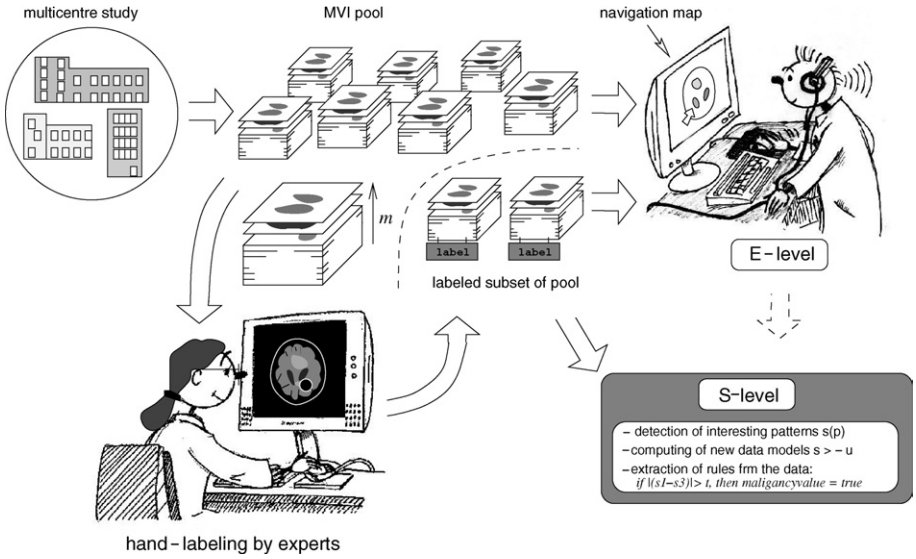

Fig. 6. In the field of medical imaging, MVIs are recorded in clinical applications and multicenter studies. Some of the data are evaluated and labeled by an experienced expert (e.g., a radiologist). The entire image pool is analyzed to maximize the diagnostic value of the imaging technique, which can be achieved by finding hidden rules in the data.

learning are applied. If background knowledge is available, a more supervised analysis can be applied, i.e., the meta-label can be used to find interesting class specific patterns.

3.2. E-level: visualization and sonification

In the E-level, the user is provided by a browsing interface, displaying a navigation map of one or several MVI(s). The navigation map supports the user to move *in information (or physical) space based on the interpretation of a mental model and/or externalized data* [67]. In the map, the user selects one ROI using a pointing device and activates a display of the ROI's parameter vector $\mathbf{u}^{(i)}$. To support the user in the E-level, methods are needed to display the navigation map and/or the vectors $\mathbf{u}^{(i)}$ appropriately. The general problem to display quantitative information with standard computer hardware has been perfectly characterized by Tufte [68]:

"...the essential dilemma of computer display: at every screen are two powerful information processing capabilities, human and computer. Yet all communication between the two must pass through the low-resolution, narrow-band video display terminal, which chokes off fast, precise, and complex communication."

The basis of the navigation map is a low-dimensional image $N(\mathbf{p}) \in \mathbb{R}^b,\ b \leqslant 3$ that is computed by applying dimension reduction or segmentation. To display this map, the values $N(\mathbf{p})$ need to be assigned to graphical display parameters $\gamma(\mathbf{p})$, in most cases a color value, as suggested by [9]. If the color scale is computed randomly, a user's attention might be driven to regions of high contrast that result from the visualization but not from the m-dimensional data structure. To avoid this, one has to claim that the color mapping must preserve the topology of the data. In other words, the patterns of two regions must be perceived similar to the degree of their similarity in the signal space (according to a chosen similarity measure, e.g., the euclidian distance). But the perception of color and brightness is of such complexity, that this assignment is hard to bring in accordance to the characteristics of humans' psychophysical properties. Although the application of color scales have been subject to several studies [69–71], the problem has not been discussed in the context of MVI visualization on a general basis. Uni- as well as multivariate scales have been proposed [71]. While univariate scales (like, e.g., a gray scale) lack in the perceived dynamic range, multivariate scales can convey different levels of information [69,71].

Exploring the navigation map, the user selects ROIs and analyzes the m-dimensional content. To this end, the parameter vector $\mathbf{u}^{(i)}$ must be displayed to the user by methods from the field of information visualization, to enable a formation of an internal model of the MVI data [67]. Any display must meet the following terms, to be applicable in the general framework of interactive MVI analysis:

Compactness. Display and visual inspection should not take too much time to enable exploration in appropriate time. It also has to allow the display of parameters of several selected regions.

Extensibility. The display technique should not be restricted to d-dimensional patterns and in principle has to be extensible to additional parameters.

Similarity. Displays for biological parameters of two regions must be perceived similar or different, corresponding to their *distance* in the parameter space. The distance in the d-dimensional parameter space can be measured using a metric function (e.g., an Euclidean distance).

Stability. The display should not change drastically in case of missing values.

Identity. Objects with identical biological parameters must be identically displayed. To this end, a normalization and thresholding procedure is applied to the signal values.

The straightforward way to graphically display the d components of $\mathbf{u}^{(i)}$ according to the above terms, in following referred to as CESSI terms, are so called *glyphs* or *icons*. To display the parameters of a ROI, standard glyphs can represent up to eight parameters by glyph location (3), size (1), color (3), and opacity (1). The standard glyphs are circles, triangles, boxes, diamonds, crosses in 2D and spheres, tetrahedrons, and cubes in 3D. In addition to this limitation, the glyphs should be designed to can be held in the perceptual working memory of the user [72]. So the number of displayed parameters is limited too strictly, if one keeps in mind the complexity if biological function and molecular and cellular interaction. Envisioning the large number of biomedical parameters that can (and will be) measured simultaneously we realize the need for increasing the comprehensiveness of glyphs. This can be achieved by (a) methods for parameter selection and reduction or (b) advanced glyphs. The task (a) can be solved by applying methods for dimension reduction from the field of pattern recognition and machine learning. One class of approaches select those features from the data set, that contribute most to partitioning the data set into different classes, i.e., have strong discriminative power. This can be achieved by iteratively increasing or decreasing the set of selected features according an optimization criterions, for example, the within-class variance and between-class distance, Another class of approaches computes lower-dimensional projections of the data applying PCA or ICA. Although these methods are motivated from a statistical point of view, the obtained results suffer sometimes from a considerable lack of interpretability. To achieve (b), only a small number of approaches have been proposed. In [73], the authors address the problem to increase the comprehensiveness of glyphs and propose a system for customized glyph generation. Their procedural shape generator is an interesting and promising approach that allows the representation of up to 18 parameters. Similar approaches have been proposed by [74,75]. Earlier works propose so called *stick figures* [76] in a graphical visualization of multivariate image data and much earlier the famous *chernoff faces* [77]. Their parameters are coded to features of a face cartoon (for example, length of nose and orientation of brows). Chernoff faces are suited to show trends in data (living quality [78], economical conditions [79]) through their emotional expression and shape. Nevertheless, their successful application depends on a clear interpretation of the patterns as positive or negative. Which makes them not suitable for most biomedical applications. There, such a categorization of the data can hardly be defined, or frankly speaking: "There is no clear categorization for *good* or *bad* cells." Advances and discussions of new approaches for graphically rendering biological parameters $\mathbf{u}^{(i)}$ of ROIs are still exceptional.

An alternative to the graphical approach are so called *sonifications* of parameter vectors $\mathbf{u}^{(i)}$, i.e., the presentation of data using sound [80,81]. Since humans have high developed skills in memorizing, discerning, and comparing auditory patterns the parameters can be rendered by sound in so called *ear-cons*. In the majority of approaches, this is realized by mapping the parameters to sound attributes like the pitch, loudness, roughness, brightness, duration, and reverberation of a piano tone. Even if this approach has already been applied quite successfully and it obeys the CESSI terms, it suffers from the problems of nonlinear acoustic scales, a lack of orthogonality and that musically untrained listeners have considerable disadvantages. The latter can be compensated by a sonification approach called *artificial words* [82]. A concatenative synthesis of diphon sequences is used to display a binary vector and a diphon becomes the acoustic marker for one variable. It is straightforward to see, that this approach obeys the CESSI terms well, since we are highly trained to process similar stimuli in real speech sounds.

Since humans are have outstanding perceptual skills and can process multisensory information with remarkable stability in parallel, it is likely that the combination of visual and auditory display has potential, as also claimed by the *dual coding* theory. However, although some works report an increased evaluation performance for subjects that are provided with multimodal display [83–85], we reported no effect in evaluation accuracy but even an increase in evaluation time [82]. On second thought, this contradiction to the other studies is not surprising bringing in mind the large numbers of degrees of freedom in designing the auditory display *and* the way of combining it with a visual display. Although it is reasonable to use multimodal displays for MVI exploration, much too less applications of such displays are reported and discussed in the literature.

3.3. S-level: clustering, learning, and classification

In the S-level, two different questions can now be asked to the data: Which features do different ROIs from one group share? Which features separate two groups of ROIs from each other?

Consider for example the $\mathbf{u}^{(i)}$ from the MVI sets of two tissue samples, one is treated with a drug and the other one is the non-treated control sample. The parameters are extracted from the MVIs and collected into a data base $\Gamma = \{(\mathbf{u}^{(i)}, y)\}$. The meta-label can be set to $y = 1$ if $\mathbf{u}^{(i)}$ is extracted from a treatment MVI sample and $y = 0$ for those from the control MVI. The question is: Which components are changing under the applied treatment? In the machine learning community, this problem is referred to as *feature selection*. In the beginning of biomedical multivariate imaging, standard statistical tests were applied [86] to find significant correlations between singe channel signals, i.e., features and the labels. Nevertheless, for a growing number of imaging parameters and less clearly defined labels, the application of standard statistical tests fail to give a comprehensive view on the data set. Thus, machine learning methods have been considered, the methods comprise different clustering and classification algorithms, probabilistic approaches, and feature projections and an overview has been recently published [87]. Since in most cases, the meta-labels of the MVIs are evaluated, the approaches can be regarded as *supervised* approaches.

Within the last 10 years, kernel based methods have been object of much research effort and gained remarkable popularity in the field supervised learning. The most prominent algorithm among these is the support vector machine (SVM) proposed by Vapnik [88] for binary classification. The community is just starting to consider SVMs for MVI analysis. In [89], it could be shown, that SVM can use multichannel information for improved prostate cancer detection. However, the authors also report good performance if Fisher linear discriminant is applied, which is much easier to train and has the advantage of interpretability concerning feature selection. In the field of biomedical informatics, multilayer perceptrons (MLP) are still the most widely used supervised learning architecture [90] and is reported to reach performances comparable to the SVM. One advantage of the MLP is also that some approaches are already proposed to extract rules from the trained weights [91]. Nevertheless, since SVMs have been applied to the task of pattern recognition, applications to the field of feature selection in biomedicine have been proposed recently [92].

Each if the supervised approaches has some steerable parameter, for example, the number of prototype vectors k in k-means clustering or a network topology. To find suitable parameterizations of the method, one has to be provided with a MVI data set, that comes together with some knowledge about the features, i.e., meta-labels, which is usually referred to as the *ground truth*. This knowledge defines one correct output of the S-level and can be used as a ground basis for tuning the parameters. Without this ground truth data mining result, yet powerful feature selection algorithms can not be evaluated and tuned. Since the parameterization of the algorithm is a crucial problem in the application of ML methods in the S-level, the question for evaluation criterions and benchmark data sets must be addressed in the following section.

4. System evaluation

In the development and evaluation of algorithms for image analysis, the discussion of new approaches is often based on the application on benchmark datasets. A comprehensive collection of such sets can be found at the *Computer Vision Homepage*.[2] Most of these image data sets are recorded in an experimental set-up, showing faces, toys, fingerprints and traffic scenes. A limited number of data sets show synthetical data for example to study texture, motion, and stereo vision. In the field of biomedical image processing, benchmark data sets concentrate again on macrobiological structures like mammograms,[3] gastrointestinal video endoscopy,[4] and MRI/CT.[5] The lack of images from the microbiological domain in general and MVI approaches in particular has several reasons: First, in microbiology the the imaging hardware settings are not integrated standardized products like in the macrobiological/medical domain. Thus, it may be awkward to find one data set, that is representative for all. Second, the biomedical researchers in this field do not share their micrographs easily with others because of competition and proprietary rights problems. Above all the last one, if the images content is settled in the field of drug discovery. Additionally, the dataset must contain a *ground truth* (or *gold standard*), i.e., a numerical expression of the correct evaluation result. For example, in case of a segmentation task, this would consist of a label image. In case of an object detection task, it would be a list of correct referential object positions. In the common case, such a *ground truth* is not available and must be simulated by a manual data evaluation by a human expert. But it is a well known fact, that in biomedical imaging, such human evaluations are expensive and error-prone [53,93,94,48,95,96]. The processing of synthetical MVIs (or phantom images) [97,61] is a promising loophole, because the usage of synthetical micrographs implies the supplements with a correct gold standard. Third, some MVI approaches are rather modern and imaging protocols need to be standardized first, before collecting benchmark data.

[2] http://www-2.cs.cmu.edu/cil/v-images.html.
[3] http://marathon.csee.usf.edu/Mammography/Database.html.
[4] http://www.gastrointestinalatlas.com.
[5] http://www.nlm.nih.gov/research/visible/visible_human.html.

5. Conclusion

The development and application of multivariate imaging in biomedicine is a rapid evolving field. The analysis of large sets of MVIs will become fundamental for diagnostic practice and scientific research, from the micro- to the macrobiological level. Reviewing proposed methods along a two level analysis framework, we are surprised to observe, that computer science is not really well prepared to provide suitable methods to for MVI data. It seems apparent, that progress in the field would be accelerated, if researchers and engineers working in biomedical MVI analysis would organize a MVI analysis community to identify fundamental problems across single particular applications and propose terms for system performance and accuracy. Particularly benchmark problems and data sets need to be installed to help researchers evaluating, developing, comparing, and discussing their methods, which holds for all aspects of data mining, from image processing to multimodal display. More than this, it would be a prerequisite for the application of more complex models of data structure analysis. A big step forward would be some KDD (knowledge discovery in databases) or visualization competition (like this year's IEEE Visualization contest[6]) with a primary focus on biomedical images or MVIs. Additionally, display techniques need to be analyzed on a more integrated, multimodal level, and analyzed on a psychophysical level. Still, discussions of integrated systems of multimodal display, like in [98] are exceptional.

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